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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,843	PELED ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *401,411,412,414,416-419,422-424,437,438,462 and 464-467* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *401,411,412,414,416-419,422-424,437,438,462 and 464-467* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04-23-2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of claims. Claims 401, 411, 412, 414, 416-419, 422-424, 437, 438, 462 and 464-467 are currently pending. Claims 401, 411, 412, 414, 422 and 462 have been amended and claims 463 and 468 have been cancelled by Applicants' amendment filed on 06-18-2008.
3. The examiner notes that a typographical mistake was inadvertently made in the rejection of claim 411 under 435 U.S.C. 102(b) as being anticipated Brown et al., (US Patent Number 5,945,337, Date of Patent Aug. 31, 1999) as evidenced by the description of claim 41,1 at page 5 of the previous office action, drawn to "a transplantable hematopoietic cell preparation comprising and expanded population of CD34+ hematopoietic stem cells. Thus it is claim 411 and not claim 412, drawn to a method, the claim rejected under 435 U.S.C. 102(b).
4. Therefore, claims 401, 411, 412, 414, 416-419, 422-424, 437, 438, 462 and 464-467 are currently under examination to which the following grounds of rejection are applicable.

Withdrawn objections/ rejections in response to Applicant arguments or amendments

Claim Objections

Notice of Non-Compliant Amendment (37 CFR 1.121)

In view of applicants' cancellation of claims 463 and 468, objection to claims 463 and dependent 468 is rendered moot.

Claim Rejections - 35 USC § 112 (second paragraph)

In view of applicants' amendment of claims 401 and 422 to recite the proper antecent, rejection of claims 414 and 422 under 35 U.S.C. 112, second paragraph, has been withdrawn.

Rejections maintained in response to Applicant arguments or amendments.

To the extent that the instant claims are broadly interpreted to culturing a population of CD34+ hematopoietic stem cells under conditions comprising about 1.0 mM to about 10mM of exogenously added nicotinamide, the following rejection applies.

Claim Rejections - 35 USC § 103

Claims 401, 411, 412, 414, 416-419, 422-424, 437-438, 462, 464, and 466-467 remain rejected and new claims 464-467 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown R (US Publication No. 2002/0159984, Date of Publication October 31, 2002).

Response to Applicants' Arguments as they apply to rejection of claim 401, 412, 414, 416-419, 422-424, 437-438, 462 and 464, 466-467 under 35 USC § 103

At page 6 of Remarks, in contrast to the Examiner's position asserting that in the instant invention Nicotinamide is one of the culture medium components, Applicants argue that "On the basis of this (incorrect) assertion, the Examiner alleges that it would have been obvious for one of skill in the art to "optimize the ranges of concentration" of nicotinamide in the IMDM as taught by Brown, to arrive at the methods of the claimed invention". In addition, Applicants allege that "Claims 401, 411,412 and 462 (from which the remaining claims subject to the rejection depend) are amended to recite "...as compared to CD34+ cells cultured in the presence

of nutrients and cytokines without exogenously added nicotinamide, nicotinamide analog or nicotinamide derivative...", thereby further affirming the essentiality of the presence of exogenously added nicotinamide, nicotinamide analog or nicotinamide derivative to the claimed invention" . Furthermore, Applicants referred to Example 5, Figures 14-18 and Table 5, in which "expansion of hematopoietic stem cells with nicotine is compared to "controls", which include an identical medium without nicotinamide" to support " in an unequivocal manner, that ex-vivo expansion and inhibition of differentiation of hematopoietic stem and progenitor cells, according to the claimed invention, requires providing nicotinamide" [emphasis added]. Such is not persuasive.

As stated in the previous office action, Brown R. teaches a method for *ex vivo* expansion (e.g. proliferation) of a population of CD34+/CD38- cells derived from cord blood (p. 1, [0010]) comprising culturing said cell population under conditions comprising FLT3, STF, IL-I, IL-6, TPO, etc. (p. [0050]) and cytokines such as, granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony stimulating factor GM-CSF) (p. 4, [0049]) which are added to a basal medium e.g., Iscove's modified Dulbecco's medium (IMDM) for expansion of CD34+/CD38- cells *ex vivo*. The IMDM comprises various vitamins and cofactors including **nicotinamide** at concentration of 4 mg/L (i.e., 0.033 mM) (p. 3, col. 2, [0040] and p. 4, table I). Further, Brown R. discloses that essential components of IMDM can be reformulated up to 10-fold amounts (p. 4, [0045]). Indeed, the instant claims do not require any specific concentration of nicotinamide in the culture medium, further indicating that nicotinamide, at any concentration induces proliferation, substantially inhibiting differentiation. Also note, that the new limitation recited in claims 401, 412 and 462, " as compared to CD34+ cells cultured in the presence of

cytokines and nutrients without exogenously added nicotinamide" is not an active step of the claimed method, and as such does not define the attributes of the expanded CD34+ population. In so far as the data presented in Example 5, pages 137-139, the specification discloses that hematopoietic CD34+ cell cultures were initiated in the presence of a combination of 5 cytokines, SCF, TPO, FLt3, IL-6 and IL-3, with or without the following concentrations of nicotinamide: 1, 5, or 10mM for up to three weeks period. FACS analysis for stem/progenitor cells indicated substantial increase in the proportion of CD34+/CD38-, CD34+/Lin- and CD34+/(HLA-DR38-) cells in cultures treated with nicotinamide. However no such limitation are recited in the claims as written. Hence the argument is not persuasive as they rely on limitations that are not present in the claims.

At page 7 of remarks, in contrast to the Examiner's assertion "concentration of essential components of the IMDM including nicotinamide for expansion of CD34+/CD38- cells *ex-vivo* is a result effective variable depending on the desired use...", Applicants' argue that "Brown merely lists nicotinamide, along with 44 other compounds, as a component of IMDM. See, for example, Table I of Brown at page 4, left column". In addition Applicants allege that "Brown is silent with respect to the criticality of nicotinamide. In fact, nowhere in Brown is there any mention, suggestion or implication that the presence or concentration of nicotinamide is in any way associated with, critical to or important to the inhibition of stem cell differentiation or stem cell expansion, as required by the instant invention. Thus, not only does Brown not consider nicotinamide essential to the claimed culture medium and conditions, or worthy of "optimization", but one of ordinary skill in the art reading Brown would be unable to readily

recognize the importance of nicotinamide for *ex-vivo* expansion and inhibition of differentiation of hematopoietic stem cells". [emphasis added]. Such is not persuasive.

As stated in the paragraph above, the instant invention does not require any specific concentration of nicotinamide exogenously added to the CD34+ cell culture supplemented with cytokines. In other words, a culture medium supplemented with concentrations of about 4 mg/L (i.e., 0.033 mM) as taught by Brown could induce CD34+ cell expansion, absent evidence to the contrary. Indeed, Applicants have not submitted any evidence that concentrations of 4 mg/L (i.e., 0.033 mM) preclude CD34+ cell expansion. Furthermore, for the reasons already of record, Brown teaches that essential components of the IMDM including nicotinamide "are present in amount sufficient to supports the *ex vivo* maintenance, proliferation and/or differentiation of CD34+ depending on the desired use" with any of the essential components of IMDM including nicotinamide been able to be reformulated up to a 10-fold amount (p.1, [0011]; p. 4, [0045]). Thus Brown, in contrast to Applicants' arguments, clearly identifies the criticality of discovering the optimum or workable ranges by routine experimentation .Hence Applicant has presented insufficient evidence commensurate with the scope of the claims, that counters the teachings of Brown, rendering obvious the instant claims with respect to culturing conditions comprising exogenously added nicotinamide for *ex vivo* expansion of a population of CD34+/CD38-.

Claim Rejections - 35 USC § 102(b)

The present invention is drawn to a transplantable hematopoietic cell preparation comprising and expanded population of CD34+ hematopoietic stem cells.

The following is a quotation of the appropriated paragraphs of 35 U.S.C. 102 that forms the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 411 remains rejected under 435 U.S.C. 102(b) as being anticipated Brown et al., (US Patent Number 5,945,337, Date of Patent Aug. 31, 1999).

Response to Applicants' Arguments as they apply to rejection of claim 411 under 35 USC § 102(b)

At page 8 of Remarks, Applicants argue that claim "Claim 412 is amended to recite "...in the presence of exogenously added nicotinamide, nicotinamide analog or nicotinamide derivative for a culture period resulting in expanding a population of CD34+ hematopoietic stem cells while inhibiting differentiation of said CD34+ stem cells in said sample" . Moreover, applicants allege that these features are not taught by the ' 337 Patent, as Brown et al discloses "serum-free medium and disclosed methods support the "proliferation and differentiation of CD34+ cells" (emphasis added)". Such is not persuasive.

Claim 411 is a product claim drawn to a transplantable hematopoietic cell preparation comprising: an expanded population of hematopoietic stem cells propagated *ex-vivo* in the presence of an effective amount of an agent that substantially inhibits differentiation of said stem cells of nutrients, a combination of cytokines and in the presence of exogenously added nicotinamide, nicotinamide analog or nicotinamide derivative. Thought the expanded hematopoietic stem cells propagated *ex-vivo* requires culture under three specific conditions all

of which are taught by the ' 337 Patent. Whether said hematopoietic cell preparation is compared with the corresponding one propagated in the presence of cytokines and nutrients without exogenously added nicotinamide, is irrelevant to the structural attributes of the transplantable hematopoietic cell preparation as claimed.

New Grounds of Rejection

Claim objections

Claim 416 is objected to because a grammatical. Claim 416 recites " any of claim 401". There is only one claim 401. Appropriate correction is requested.

Claim Rejections - 35 USC § 102(b)

To the extent that the instant invention is drawn to methods of expanding a CD34+ hematopoietic stem cells *ex-vivo* comprising culturing said population of CD34+ hematopoietic stem cells under conditions comprising exogenously added nicotinamide to CD34+ cell cultures supplemented with cytokines resulting in expansion of CD34+/CD38- cell population without requiring specific concentrations of nicotinamide in the culture medium, the following rejection applies. Note that claims 462 and depending claim 467 are not included in this rejection because claim 462 required culture conditions comprising about 1.0 mM to about 10 mM of exogenously added nicotinamide.

The following is a quotation of the appropriated paragraphs of 35 U.S.C. 102 that forms the basis for the rejections under this section made in this Office action:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 401, 412, 414, 416-419, 422-424, 464 and 466 are rejected under 435 U.S.C. 102(b) as being anticipated Brown et al., (US Patent Number 5,945,337, Date of Patent Aug. 31, 1999).

Brown R. teaches a method for *ex vivo* expansion (e.g. proliferation) of CD34+/CD38- cells derived from umbilical cord blood (p. 1, [0010]). Brown R. discloses the presence of appropriate growth factors in the medium such as interleukins, CSF, stem cell factor, thrombopoietin (TPO), interleukin-1 (IL-I) and interleukin-6 (IL-6) which influence the rate of proliferation and the distribution of cell types in the population (p. [0049]). Moreover, Brown R. discusses that one or more of the cytokines playing a role for driving proliferation in hematopoietic cells can be added to the culture medium at different stages of the culture to alter the cell population including FLT3, STF, IL-I, IL-6, TPO, etc. (p. [0050]) and cytokines such as, granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony stimulating factor GM-CSF) (p. 4, [0049]). Note that G-CSF is a late acting cytokine. Moreover, Brown R teaches the requirements for the basal medium composition for expansion of CD34+/CD38- cells *ex vivo* including nicotinamide at concentration of 4 mg/L (p. 3, col. 2, [0040] and p. 4, table I). Though Brown et al., does not specifically disclose that expansion of CD4+ substantially inhibits differentiation, substantial inhibition of differentiation is necessarily present as the culturing conditions in Brown are the same. Note that claims 412 and 462 do not recite the limiting condition "substantially inhibiting differentiation of the stem cells *ex-vivo*". **(Current claims 401, 412, 414, 416-418, 422-424).** Additionally, Brown discloses that umbilical cord

blood as the source of HSCs contains a reduced number of stem cells compared to bone marrow as determined by enumeration of nucleated mononuclear cells and/or CD34+, indicating the presence of a mixed cell population (p. 1, [0008]), (**Current claim 417**). Furthermore, Brown discloses that "Early progenitors (CD34, CD38, HLA-DR), myeloid markers (CD33, CD14, CD45), lymphocyte markers (CD3, CD7, CDI9), red blood cell markers (glycophorin A) and megakaryocyte/platelet determinants (CD41a)" and assesses by FACS the cluster of markers CD45, CD14, CD34, CD20, CD33, CD3, CD7, CD56, CDIO, CD4, CD8 (BDIS) and glycophorin A (p. 8, [0102]), Thus Brown does not explicitly discloses diminished expression of CD33, CD14, CD3 and other surface makers, reduction of said markers is inherently anticipated in an expanded population of CD34+ cells as CD33, CD14, CD3 makers identify differentiated stem cell populations (**Current claim 419**). Furthermore, Brown R. exemplifies cultures of the bone marrow CD34+ enriched population showing CD34+/CD38- cells with significant expansion at day 3, 7 and 14, in the absence of serum and low concentrations of IL-3, IL-6 and SCF (p. 10, [0119]) (**Current claims 419, 464, 466**).

Thus by teaching culture conditions including exogenously added nicotinamide to CD34+ cell cultures supplemented with cytokines resulting in expansion of CD34+/CD38- cell population, Brown anticipates the claimed invention

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 419 and 465 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language.

Claim 419 which depends on claim 418 recites "said expanded hematopoietic cells". However, claim 418 only refers to a "stem cells". Thus there is not a proper antecedent bases for said expanded hematopoietic cells as recited in claim 419. As such, the metes and bounds of the claims cannot be determined.

Claim 465 depends on claim 411 and recites "the method of claim 411". However, claim 411 is drawn to a transplantable hematopoietic cell preparation and not to a method. As such, the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 401, 437 and 438 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown R (US Publication No. 2002/0159984, Date of Publication October 31, 2002) in view of Banasik et al., (1992, JBC, pp. 1569-1575, of record).

Brown R. teaches a method for *ex vivo* expansion (e.g. proliferation) of CD34+/CD38- cells derived from umbilical cord blood (p. 1, [0010]). Brown R. discloses the presence of appropriate growth factors in the medium such as interleukins, CSF, stem cell factor, thrombopoietin (TPO), interleukin-1 (IL-I) and interleukin-6 (IL-6) which influence the rate of proliferation and the distribution of cell types in the population (p. [0049]). Moreover, Brown R. discusses that one or more of the cytokines playing a role for driving proliferation in hematopoietic cells can be added to the culture medium at different stages of the culture to alter the cell population including FLT3, STF, IL-I, IL-6, TPO, etc. (p. [0050]) and cytokines such as, granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony stimulating factor GM-CSF) (p. 4, [0049]). Note that G-CSF is a late acting cytokine. Moreover, Brown R teaches the requirements for the basal medium composition for expansion of CD34+/CD38- cells *ex vivo* including nicotinamide at concentration of 4 mg/L (p. 3, col. 2, [0040] and p. 4, table I). Though Brown et al., does not specifically disclose that expansion of CD4+ substantially inhibits differentiation, substantial inhibition of differentiation is implicitly necessary, absent evidence to the contrary, as the culturing conditions in Brown are the same.

Brown does not specifically teach benzamide as the nicotinamide analog.

However, at the time the invention was made, Banasik et al., discloses specific inhibitors of ADP-ribosyltransferases, specially poly(ADP-ribose). Banasik et al., illustrates in Table 1, at page 1573, the comparative effect of various compounds on inhibition of poly(ADP-ribose)

synthetase activity including nicotinamide (number 27), benzamide as a potent inhibitor and numerous benzamide analogs (Banasik et al., JBC, p. 1570, col. 1, paragraph 2; Table 1, numbers 22, 45, 103, 113, 77 and others).

Thus, it would had been *prima facie* obvious for the skilled artisan to substitute nicotinamide by any benzamide or benzamide analog because the function of both compounds were well known in the art as inhibitors of poly(ADP-ribose) synthetase activity. One of ordinary skill in the art could have substituted one known element for another and the result of the substitution would have been predictable. Thus the combination of Brown R and Banasik et al., obviate the instant invention.

Conclusion

Claims 401, 411, 412, 414, 416-419, 422-424, 437, 438, 462 and 464-467 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Maria Leavitt/
Maria Leavitt, PhD
Examiner, Art Unit 1633